stated in the protocol. This implies first-hand knowledge of the expected caries rate in the subject pool. It is desirable that the subject pool reside within a single, albeit large, community. If this be the case, then concerns about pooling of data from several widely-dispersed communities fail to arise. Also, within that pool of subjects, it is desirable to have minimal mobility so that the "dropout rate" will be low. The pool of subjects should be selected in order to minimize dental "noise" from unwanted sources. Obviously, a community in which another trial is planned or is in progress should be avoided. Likewise, the selection process should exclude communities which plan to initiate projects affecting dental health during the trial. Thus, a community which was planning to implement water fluoridation would be excluded, as would a community in which a new dental center was planned.

A mechanism for recruiting the subjects should also be in place. A strategy for recruiting should include mechanisms to inform the community of the trial and the potential health benefits and risks from it. (In the process of recruitment, the nature of the trial must be made crystal clear to the potential subjects, so that they understand the risks and benefits accruing from participation in the trial. Once the subjects understand the nature of the trial, a statement of informed consent should be obtained in which the subjects agree to participate under the conditions of the trial.) In order to make a decision to proceed, researchers should establish access to the required pool of subjects.

(3) *The examiner.* — The examiner determines the progression of caries during the trial by examining each subject for caries. This is done using methods specified in the protocol, and usually visual-tactile and radiographic examinations are included. The examiner must be available for the duration of the trial. In the selection of an examiner, it would seem prudent to select one who in the past has shown the ability to detect the difference stated in the hypothesis. If this aspect is disregarded, it is conceivable that the protocol could have a built-in bias toward false acceptance of the null hypothesis. In other words, selection of an examiner who was unable to detect the difference stated in the hypothesis could result in the generation of data which would indicate that control and product have similar efficacies when, in fact, the product was actually either more or less effective than the control.

A minor, but often troublesome, corollary to the selection of an examiner is a place for the examiner to work. This could also serve as a distribution site for the product. Plans should be made so that the examiner can function smoothly with a minimum of interference.

(4) *Data processing.* — The examiner generates data which must be processed and analyzed statistically so that the hypothesis stated in the protocol can be tested. The data processing element should be in place so that acceptance or rejection of the hypothesis can occur without a question related to data handling.

(5) *Money.* — Need we say that a clinical trial that may last years and involve thousands of subjects costs a lot, perhaps in the millions, even excluding the R&D costs of the product. Before a final decision to proceed can be made, an estimate of the cost of the trial should be made, and it should be established that the probability of success of the trial is commensurate with the amount of money to be expended upon it. If this cost estimate is in order, then the decision to proceed can be made with reasonable assurance that a valid trial will be conducted.

In summary — If the product meets the criteria below, then the product should be deemed worthy of clinical trial:

- Anti-caries efficacy,
- Safety,
- Benefit/risk assessment,
- Acceptance by subjects,
- Manufacturing,
- Supply and distribution, and
- Cost-effectiveness.

The clinical trial mechanism should be deemed ready when the following criteria have been met:

- Protocol/hypothesis,
- Subjects,
- Examiner,
- Data processing, and
- Money.

Once it has been established that the above criteria are met, then a decision to proceed is in order. Fulfillment of the stated criteria should carry with it reasonable assurance that a valid estimate of the anti-caries efficacy of the product will be obtained.

How Is It Decided When to Conduct a Clinical Trial?: Discussion of Dr. Briner's Presentation

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The process of deciding whether and when to begin a clinical trial can be examined from several perspectives. Dr. Briner has enumerated some of the practical considerations which are involved in this decision. I agree that every point he mentions ought to be explicitly addressed before a trial is undertaken, and, since I am not going to engage in nitpicking, I shall generally let his suggestions stand unchallenged, although I have a few amendments to some of his remarks.

I would like to approach the question from a slightly different standpoint, and suggest that, when the time has come to think about a clinical trial, we really ought to concentrate on three major questions:

- Is it likely that a trial can be carried out which will provide an unequivocal answer to the question of interest?
- Is the answer to the question worth having?
- Is it ethical to conduct a trial to get the answer?

I will comment briefly on each of these points.

- *Is it likely that a trial can be carried out which will provide an unequivocal answer to the question of interest?* — This question refers to the design of the trial, and it subsumes most of the criteria of which Dr. Briner spoke. What needs emphasis, however, is that the design of a clini-

cal trial today involves a different, or at least an expanded, set of constraints than was the case ten or 20 years ago.

Take, for example, the question of number of subjects. It is true that this is determined jointly by the size of the treatment-control difference of interest, and the expected mean and variance of the caries increment. However, we cannot overlook the fact that, these days, we are often interested in comparing a new agent to one of established effectiveness – that is, we usually wish to detect much smaller differences than we did in the past, when inactive placebos provided the basis for comparison.

The size of study groups estimated to be needed to detect small differences can easily become so large that, for economic and logistical reasons, inadequate provisions are made for likely attrition of subjects. Where the size of the required experiment is very large, there is a temptation to "take a chance" and forego normal margins of safety. Perhaps we should, instead, reconsider the likelihood that the trial will eventuate in a clear-cut and useful result. If it does not, we have accomplished nothing – indeed, we may have done harm, from several points of view.

A related problem arises with regard to selecting a population wherein the expected increment of caries in the control group will be suitable for clear-cut hypothesis testing. Frequently, I fear, there is not much known about the expected increment in the control group, beyond reference to some shaky retrospective prevalence data combined with a large measure of hope. In the light of recent downward trends in caries prevalence among children, this problem becomes even more serious. At the least, we had better plan to spend the time and money to collect reliable contemporary data on caries incidence before we decide to initiate a trial. At most, when confidence is lacking in our estimate of expected incidence, we might reconsider whether the trial is really adequately designed, at least for the population we planned to use.

I should add that, because of our "modern" problems of obtaining adequate sample size and adequate incidence of disease, I would not expect, as Dr. Briner urges, that we will be able to conduct future trials within single communities. The desirability of doing so seems to have become a bit outdated. We will have enough difficulty in finding groups of the size required which are reasonably homogeneous with respect to relevant predisposing factors, without insisting that they live within some arbitrary political boundary.

Other examples could be raised. The point is simply that the exigencies of the real world will frequently and seriously reduce the likelihood that a contemplated clinical trial will yield a clear result. This must be recognized in advance. It may require a new design, a new population, or a new decision about whether to begin a trial.

- *Is the answer to the question worth having?* – Certainly this is the most important consideration when thinking about whether to begin a clinical trial. There is strongly suggestive evidence in the literature that it is not always given due weight in research planning.

Is it, for example, worth a long, expensive clinical trial to establish that some new fluoride compound is approximately as cost-effective as one already in general use? Or that some regimen of oral hygiene reduces plaque scores by 25% (without reference to its effect on disease)? There are more than a few examples of these and similar "facts" established by actual clinical trials.

In some cases, perhaps, the investigators have been guilty of inadequate design or excessive faith, as mentioned in my earlier remarks. In others, though, it is clear that there was no good prior evidence to suggest that the end result would be any different than it was.

Of course, I realize that some may mount persuasive arguments for the value of such undramatic, though positive, results. I suggest, however, that the value of demonstrating that a new preventive method is as good as, or marginally better than, an existing one ought to be balanced against the current cost in time, money, and manpower to carry out the trial.

I stand firmly with Dr. Briner in stating that there should be prior evidence of efficacy and cost-effectiveness of a new agent before it goes to clinical trial. Indeed, I will go further and say that there ought to be very good reason to believe, from both animal experimentation and biologic theory, that the new agent will prove substantially *more* cost-effective than existing ones of the same category. This seems to be only prudent. Yet it is related to another interesting question:

- *Is it ethical to conduct a trial to get the answer?* – Dr. Heifetz will discuss this topic more thoroughly, but I wish to comment on it also, because there is one aspect of the ethical issue that I find especially perplexing.

I have just argued that we should have compelling pre-clinical experimental and theoretical evidence for the probable efficacy of an agent before embarking on the expensive and complex enterprise that a clinical trial has become. This argument may be described as an economic one. At the same time, however, one could fairly ask whether it is ethical to conduct a study wherein some children will be deprived of a new agent which we believe, with some degree of confidence, to be superior to the control. A variation on the same theme is the situation in which we wish to satisfy doubters (or the Food and Drug Administration) by the conduct of a replicate trial of an agent which has already been successfully tested. Is this ethical? I do not know the answer; to me this has the makings of a dilemma, in the strictest sense. Perhaps the solution depends partly on the degree of prior confidence we have about the new agent but, of course, this concept is inherently unscientific. The problem is not Bayesian – not statistical at all. The problem is ethical. I can conceive of circumstances where the results of animal studies, together with theory, together with inferences from previous clinical experiences, would be sufficient to persuade me that a classic "definitive" trial of an agent was not necessary and should not be done. This subject is complicated and somewhat esoteric, and causes conflict with traditional experimental philosophy. Nevertheless, the question is real, and I predict that we will have to face it frequently in the future.

The kinds of problems to which I am referring are less concrete than those we have learned how to solve. They might be regarded as elements of a new sort of research that could be called the "modern" caries clinical trial – modern, in the sense that the problems arise both because of changing circumstances in the populations in which our research must be conducted and, importantly, because of changing public perceptions about the desirability of human experimentation.

There will be occasions when a protocol statisfies all of the classic criteria of good design of which Dr. Briner spoke, but may not justify an affirmative decision to proceed. We will, of course, have to continue to conduct well-controlled clinical trials to obtain satisfactory answers to our questions. But to do so, we may have to acquire a much greater insight into the economics, ethics, and even the philosophy of clinical trials than was required of us a decade ago.

Ethical Considerations and Study Design

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Many types of ethical dilemmas must be considered in the conduct of clinical trials of dental caries preventives. Published regulations and reports on the protection of the rights and welfare of human subjects in clinical research emphasize important requirements of informed consent. For the purpose of this Conference, this paper focuses on ethical considerations as they affect the design and analysis of clinical trials.

It is patently unethical to carry out research that is scientifically unsound. Misleading or incorrect results produced by faulty or improperly designed studies may have dire human consequences. What can be more damaging to the advancement of medical knowledge than research that fosters the use of ineffective therapeutic agents or that misses the detection of potentially effective ones?

Many aspects of study design offer potential pitfalls that can lead to erroneous results. I propose to limit my discussion to just three: statistical power considerations, self-selection of participants, and retrospective controls.

Statistical power considerations.

Most investigators are familiar with the concept of α error (a false conclusion of efficacy) in clinical trials. The complementary mistake of β error (a false conclusion that no efficacy exists) is not as well-known. The statistical power of a test, or $1-\beta$, is the probability of detecting a real (statistically significant) and important (clinically significant) effect when it is present. For most trials, an acceptable power level is 80% or greater. Considerations of statistical power come into play in "negative" trials, when an investigator has concluded that two competing treatments are equivalent or not different because a high P value (>0.05) is computed for the observed difference. However, before one accepts this conclusion, the statistical test's power to detect an important clinical difference correctly must be known. If, for example, the test had only a 60% chance of correctly finding a 20% difference at an α level of 0.05, the investigator should be unwilling to risk accepting the null hypothesis by concluding that the difference is "insignificant". Moreover, though bracketing zero, if the 95% confidence limits for the true percentage reduction of the sampling included a 20% reduction, even stronger doubts about the investigator's conclusion exist. Both the width of the confidence interval and the power of the test attest to the adequacy (or inadequacy) of the sample sizes used.

Investigators should consider the power of statistical tests when determining the balance of groups on prognostic baseline characteristics for initial participants and for those who complete a clinical trial. When there is suspicion of imbalance among the groups, an α value of >0.05 alone cannot be accepted as confirmation of their comparability. Additional evidence of an acceptable power level or at least an indication that the 95% confidence interval does not bracket differences of important clinical dimensions is required.

A 1978 report[1] that analyzed 71 "negative" clinical trials published in 20 different medical journals found that half had a greater than 74% chance of missing a clinically important difference because of insufficient sample sizes. The problem of using sample sizes that are too small to offer a reasonable chance of correctly rejecting the null hypothesis has not affected most trials of cariostatic agents to date. Relatively large caries increments and substantial differences between treated and untreated study groups have helped us in this regard. However, the days when we can expect a reasonably high caries incidence (two or more DMFS/child/year) during the relatively short period of a clinical trial and differences of 25% or larger between study groups are probably past. As discussed more fully later in this paper, dental caries has declined dramatically in many countries. A decline in caries prevalence denotes a decline in caries increment, and the lower the caries incidence in a two- to three-year clinical trial, the greater the relative variability of the data or the co-efficient of variation (C.V.).[2] Concerning measurable effects, ethical constraints today have shifted interest to comparisons of standard with new therapies rather than of therapies with controls, thus decreasing expected differences between groups. Both of these factors demand larger sample sizes for current clinical trials in order to ensure sufficient power. For example, increasing the C.V. from 1 to 1.25 and reducing the expected treatment difference from 25% to 15% necessitates more than a five-fold increase in the number of subjects required *per* group, assuming that all other parameters of the data remain constant.[3]

The conclusion is unavoidable: Today's investigator must be concerned about statistical power both in planning a trial and during its course, when loss of participants may become a factor. No doubt, investigators will not always agree on what constitutes a clinically important difference for a given comparison of alternative therapies, and they will also differ on the risk that they are willing to take of missing it. But to start or continue a study when the available sample sizes indicate virtually no chance of detecting a treatment effect unless it is truly massive is difficult to justify. Such a study is scientifically useless, may expose subjects to discomfort or possible risk with little chance of producing correct results, and wastes valuable monetary and personnel resources.

Reports of studies are incomplete that ignore information on statistical power, particularly if no difference has been found between test agents. The editors of many scientific journals require a statement of appropriate compliance with informed consent procedures. They should also insist that investigators cite the probability for correctly detecting an important clinical effect with the sample sizes used. In short, it is a breach of commitment to goals of conducting and publishing ethical research if investigators and editors, respectively, are remiss in seeing to it that statistical power considerations are included in reports of randomized clinical trials.

Self-selection of participants or compliance bias.

A recent article by the Coronary Drug Project Research Group in the *New England Journal of Medicine*[4] alerts the reader to the bias that can be introduced in a randomized clinical trial when patients are removed from the analysis

because of poor adherence to the prescribed therapy. The research group found a substantially and significantly lower mortality rate among good adherers who took the prescribed number of pills per day than that found among poor adherers. But, before reading into these results any suggestion of efficacy, the appropriate corresponding comparison was made in the placebo group. Surprisingly, the same difference was detected between patients who complied well or poorly with taking the placebo pills. Attempts to adjust the findings in the placebo subgroups for the unequal prevalences of known prognostic baseline characteristics accounted for only a small part of the observed difference between good and poor adherers. Evidently, adherence to treatment had defined subgroups with major differences in characteristics that influence the prognosis of the disease. Because the reasons for, in effect, the self-selection of patients into subgroups of good and poor adherers were unknown and confounded the results, the investigators doubted that any valid conclusions could be drawn from the study.

The potential for bias from self-selection of subjects also exists in randomized clinical trials of dental caries preventives. Particularly vulnerable are studies of self-administered agents in which patient compliance is an important factor. Investigators tend to confine the analysis to those subjects who have received an "adequate" number of treatments; the underlying assumption is that good and poor compliers differ only in the amount of therapeutic exposure. But the validity of this assumption is questionable.

We are all familiar with the bias that can occur in studies of home-use of fluoride tablets, where good compliers are mainly the children from homes providing a high degree of dental motivation.[5] Those who are able to follow the strict daily regimen for many years may also be the ones who are equally conscientious about their dietary practices, brushing habits, and regular visits to a dentist. Thus, the children who are good compliers are likely to have the least decay. Comparing the results of good compliers in the test group with those of all children in the placebo group may produce an exaggerated estimate of effectiveness. If the analysis were restricted to subgroups of good compliers in both test and placebo groups, then the results, probably of diminished effectiveness, would be valid for the subgroups under study. However, one of the main scientific (and ethical) objectives of large-scale clinical trials – the generalizability of results – has been compromised by the subanalysis of the data.

A more complex type of bias resulting from self-selection arises when prognostic characteristics of good and poor compliers differ not only within but also between groups. As a hypothetical example, consider a study comparing the effectiveness of sodium fluoride and acidulated phosphate-fluoride (APF) supplements. The study is conducted daily in school under the supervision of lay personnel. Subjects are asked to assemble in the cafeteria a few minutes before the start of classes to carry out the procedure. Because of the important topical as well as systemic benefits of fluoride tablets, children are asked to first chew the tablet and swish the resultant solution around in the mouth before swallowing it. Now suppose that because of the nature of the ingredients, particles of the APF tablet, but not the sodium fluoride tablet, impact in the pits and fissures of teeth. In the APF group, children with anatomically well-defined teeth find the impaction problem particularly annoying and tend to cooperate the least. At the end of the study, the investigator finds a poorer record of participation in the APF group, but attributes it to the sour taste of the acid tablets. To gain efficiency and to give (he thinks) the agents a fair trial, he restricts the analysis only to the good adherers. But the difference in side-effects between the two treatments which has caused the difference among good adherers is risk-related, *i.e.*, teeth with deep pits and fissures tend to have a greater susceptibility to dental decay....and the stage is set for bias.

This example, admittedly overdrawn, shows how a cohort uniquely biased by a compliance-confounded risk can arise from a seemingly reasonable subgroup analysis. In theory, it should be possible to adjust biased findings statistically for differences in prognostic characteristics of dental caries through various schemes of covariance or blocking. Unfortunately, knowledge of these disease-related characteristics is incomplete; all of the known prognostic factors combined may account for only a small fraction of the variance in incremental decay.[6]

Post hoc selection of subgroups in a clinical trial, whether defined by the subject or investigator, courts bias and may lead to erroneous results. It is thus probably safest to adopt a policy of using the results of all subjects remaining from the initial randomization. This approach offers the best chance of obtaining balanced groups with respect to both known and unknown prognostic variables related to dental decay. Removal of subjects from the analysis on the basis of some characteristic measured during the test, such as compliance, loses the advantages of the initial randomization and may invalidate the research.

Use of retrospective controls.

Although ethically desirable because all patients receive treatment, the use of retrospective controls has always been a risky approach to determining a cause-and-effect relationship. Studies of this design have many deficiencies, not the least of which is that they provide limited protection against the bias that may be introduced by secular changes that either directly or indirectly affect dental caries prevalence, *e.g.*, changes in the nature of the study population, in the level of dental care, or in the method of assessment.

But problems of this type are familiar to dental researchers, and they can often be adjusted for or controlled by adherence to careful study methodology. However, a new variable has been noted: The disease level itself has been changing markedly with time. Several epidemiologic studies have shown a declining caries prevalence in western developed countries in recent years.[7] Must we now assume that retrospectively controlled studies will inherently produce spurious results? If the findings of such studies are thought invalid and unreliable, should not such study designs be rejected as unethical?

I do not think the prospects for retrospective studies are as bleak as those pre-supposed by these questions. Scientific conclusions about the results can be strengthened by, in addition to the regular external analysis, *i.e.*, comparing the results of cohorts to the baseline population, making analyses of the internal consistency of the data. Such comparisons might include a look for specificity of treatment effect and dose-response relation.

Consider the following results from a retrospectively controlled study of our research group at NIDR. The study was initiated in the elementary schools (grades K-6) of Nelson County, Virginia, in 1972. Under teacher supervision, children daily ingested a fluoride tablet, rinsed weekly with a dilute fluoride solution, and received a fluoride dentifrice for home use. The program was extended

TABLE
MEAN PREVALENCE OF DMFS BY TYPE OF SURFACE FOR CHILDREN AGES 6-14 IN 1972 AND 1980, NELSON COUNTY, VIRGINIA

Type of Surface	Mean DMFS 1972	Mean DMFS 1980	Difference in Mean DMFS	Percent Difference From 1972
Occlusal	3.14	1.99	1.15	36.6
Buccolingual	1.73	1.02	0.71	41.0
Mesiodistal	1.45	0.20	1.25	86.2
All Surfaces	6.31	3.22	3.09	49.0

Source: Horowitz, H.S. *et al.*[8]

to the upper grades incrementally, beginning with grade 7 in 1978. In 1980, dental examinations of children ages 6-14 who had continuously participated in the program for from one to eight years, depending on school grade, showed an overall mean prevalence of 3.22 DMFS, 49% lower than the corresponding score of 6.31 DMFS for their cohorts at the baseline.[8]

To determine if there was a difference in treatment effect according to type of surface, the overall findings were separated into occlusal, buccolingual, and mesiodistal components. Results of the analysis for specificity of treatment effect are shown in the Table. It is apparent that all types of surfaces received protection, but the greatest difference, both absolute and relative, occurred in mesiodistal surfaces. Fluorides have repeatedly been shown to exert their maximum preventive effect on smooth or approximal surfaces.[9]

At each follow-up survey since the baseline scores were established, the reductions in dental caries prevalence have continued to improve: They were 18% after two years[10], 35% after four years[11], 45% after six years[12], and 49% after eight years. These sequential findings are consistent with the increasing exposure of continuous participants to the fluoride program, but they also jibe with the aforementioned decline in the prevalence of dental caries that has occurred in the United States within the same period as the Nelson County study, the 1970's.

To help sort out the possible confounding effects, the data can be analyzed for a dose-response relation. Fig. 1 shows the age-specific, average prevalence of DMFS for children 6-14 at baseline and in 1974, 1976, 1978, and 1980. The age of the children when they first began to use the preventive program at the time of each examination appears above each age-specific plot. For example, a blow-up of the plot for just the 12-year-old cohorts (Fig. 2) shows that:

In 1972, 12-year-olds were in junior high school and, therefore, missed exposure (N) to the start of the elementary school program;

In 1974, 12-year-olds were ten years of age when the fluoride program began or had been exposed for two years;

In 1976, 12-year-olds were eight years of age when the fluoride program began or had been exposed for four years; and

In 1978 and 1980, 12-year-olds were both six years of age when the fluoride program began and had been exposed for the same duration of six years.

Collectively, the findings in Fig. 1 follow a logical pattern in relation to extent of participation in the program, *i.e.*,

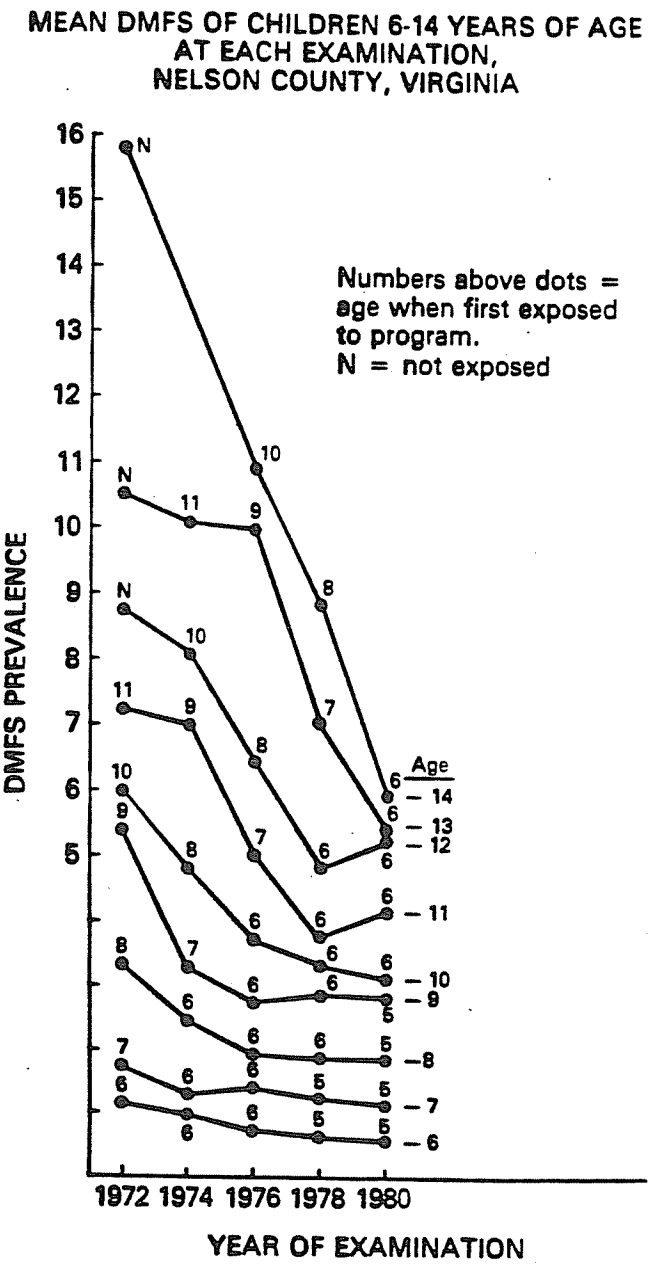

Fig. 1– Source: Horowitz, H.S., *et al.*[8]

when starting ages of exposure to fluorides are similar, there tends to be little difference in age-specific prevalence scores with time, whereas, when participation begins at an increasingly earlier age, a steady improvement in benefits among successive cohort groups is generally observed.

These internal analyses of data from a retrospectively controlled study lend validity to the conclusion that the marked decline in dental caries prevalence in Nelson County schoolchildren can largely be attributed to the fluoride prevention program. That the cohorts were followed prospectively in an experimental situation, with treatments controlled and recorded for each subject and the data collected in the same fashion by the same examiners according to an advanced plan, further strengthens the conclusions that can be drawn from this retrospectively controlled investigation.

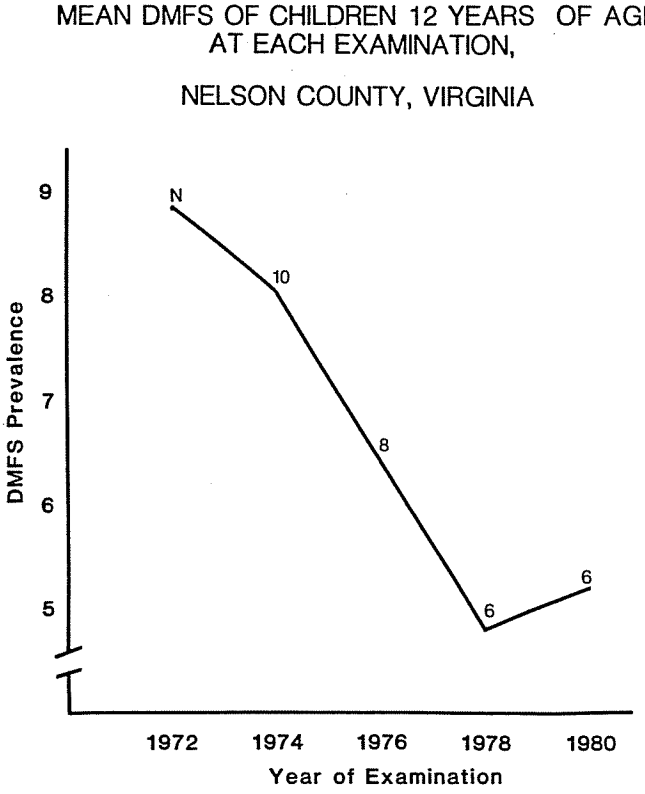

Fig. 2

At the "First International Conference on the Declining Prevalence of Dental Caries"[7], most of the evidence for the decline was derived from epidemiologic or purely observational studies that used retrospective or historical controls. Most participants agreed that the increased and widespread use of various fluoride modalities was the major factor responsible for the decline, although some voiced uncertainty because only associations can be drawn from retrospective studies. However, the more rigorous type of retrospectively controlled study in Nelson County, in which the delivery of fluorides has been formalized under experimental conditions, offers persuasive evidence to corroborate the general conclusion of the Conference. Moreover, the example of the Nelson County study provides tangible evidence that correct inferences can still be drawn from well-designed retrospective studies on the effectiveness of organized fluoride programs, despite the current decline in caries prevalence.

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